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Περιφερειακό Συνέδριο
Ελληνικής Εταιρείας Αιμαφαίρεσης

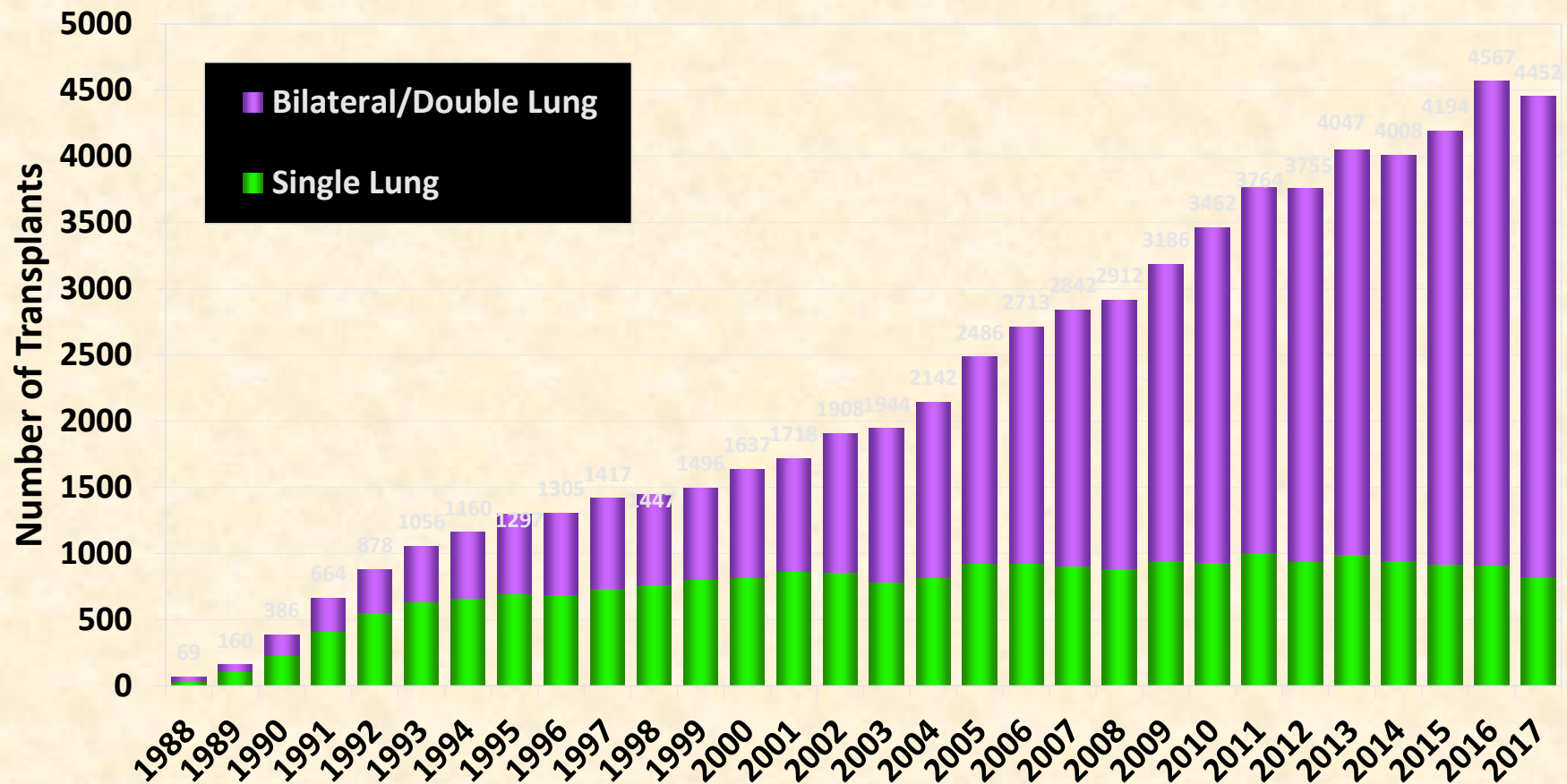
Φωταφαίρεση και μεταμόσχευση πνεύμονα

Φραντζέσκα Φραντζεσκάκη
Πνευμονολόγος-Εντατικολόγος
Β' Παν/κή Κλινική Εντατικής Θεραπείας
ΠΓΝ «ΑΤΤΙΚΟΝ»

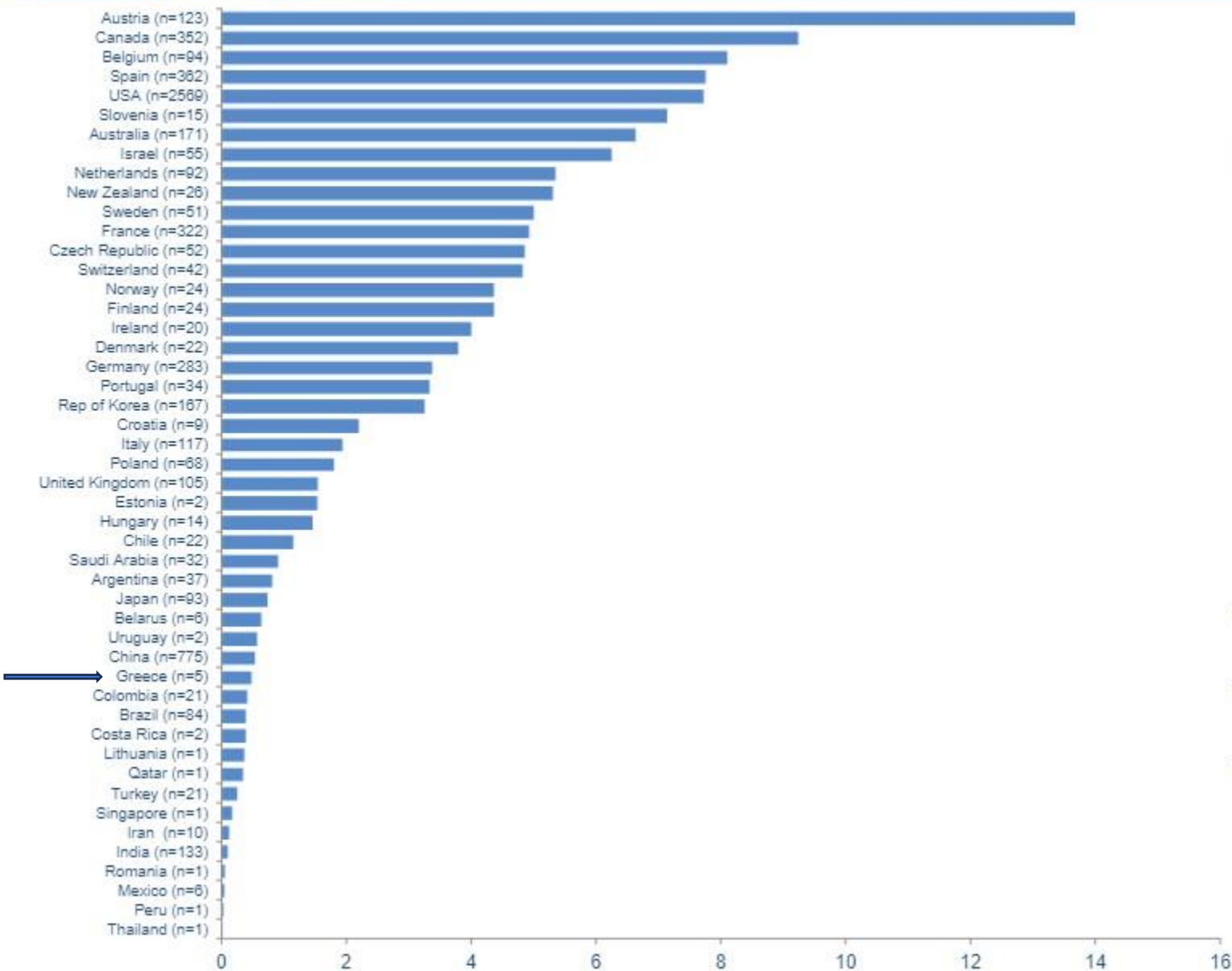


Adult Lung Transplants

Number of Transplants by Year and Procedure Type



NOTE: This figure includes only the adult lung transplants that are reported to the ISHLT Transplant Registry. As such, this should not be construed as representing changes in the number of adult lung transplants performed worldwide.



Lung transplants per million population (pmp) 2021



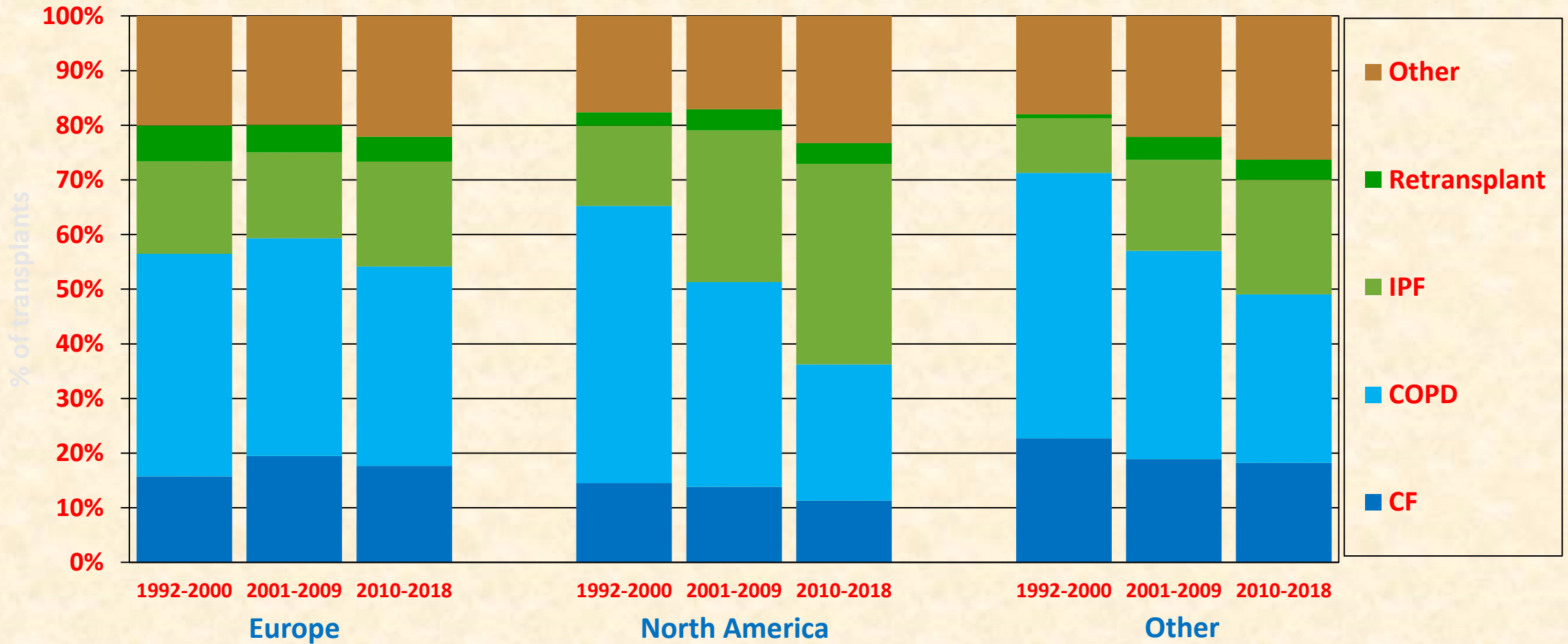
48/91 countries reported lung
transplant activities in 2021

- ✓ 6 470 lung transplants
- ✓ 8.9 % increase vs 2020
- ✓ 19 living lung transplants (0.3%)

Adult Lung Transplants

Recipient Diagnosis Distribution by Location and Era

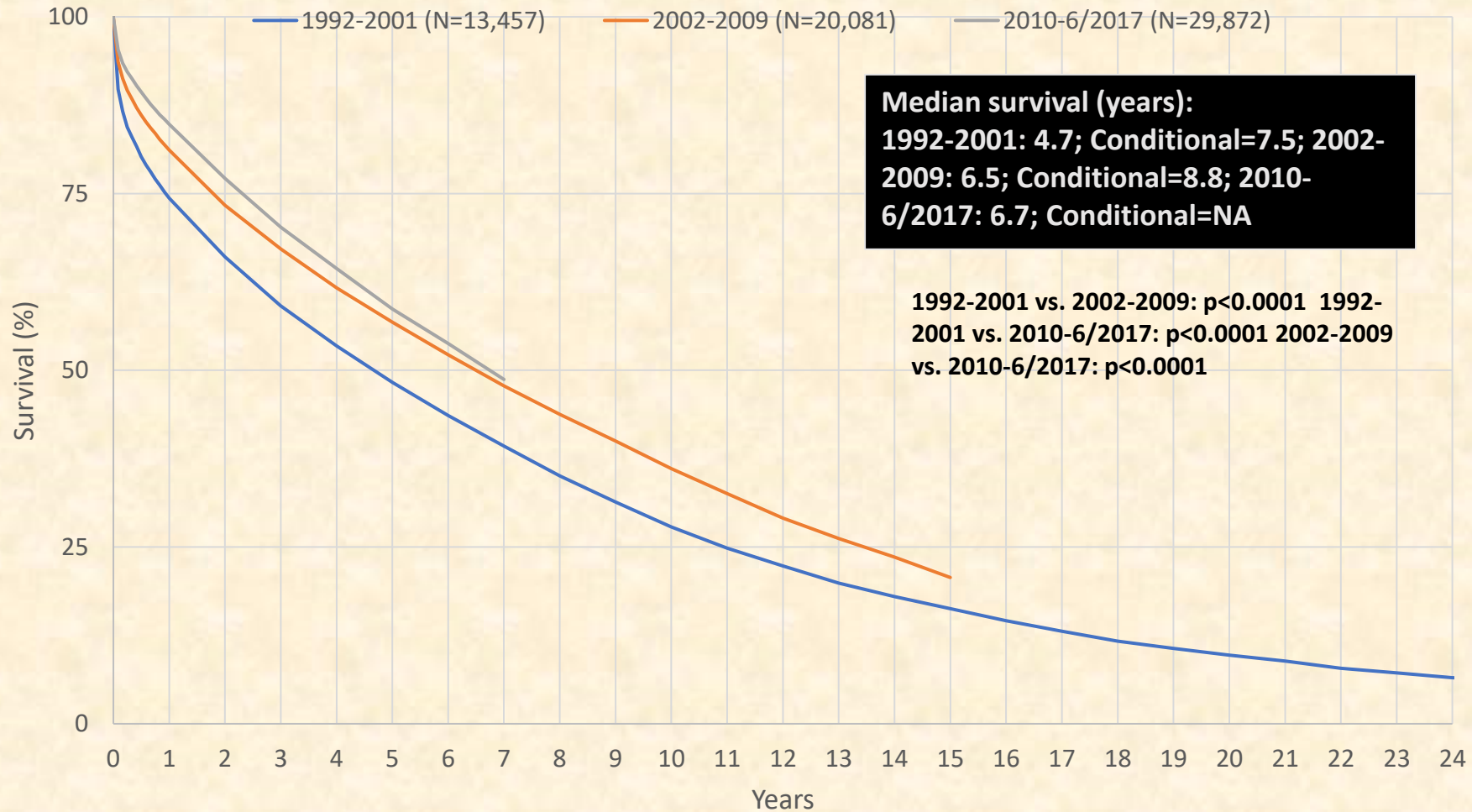
(Transplants: Jan 1992 – Jun 2018)



Adult Lung Transplants

Kaplan-Meier Survival by Era

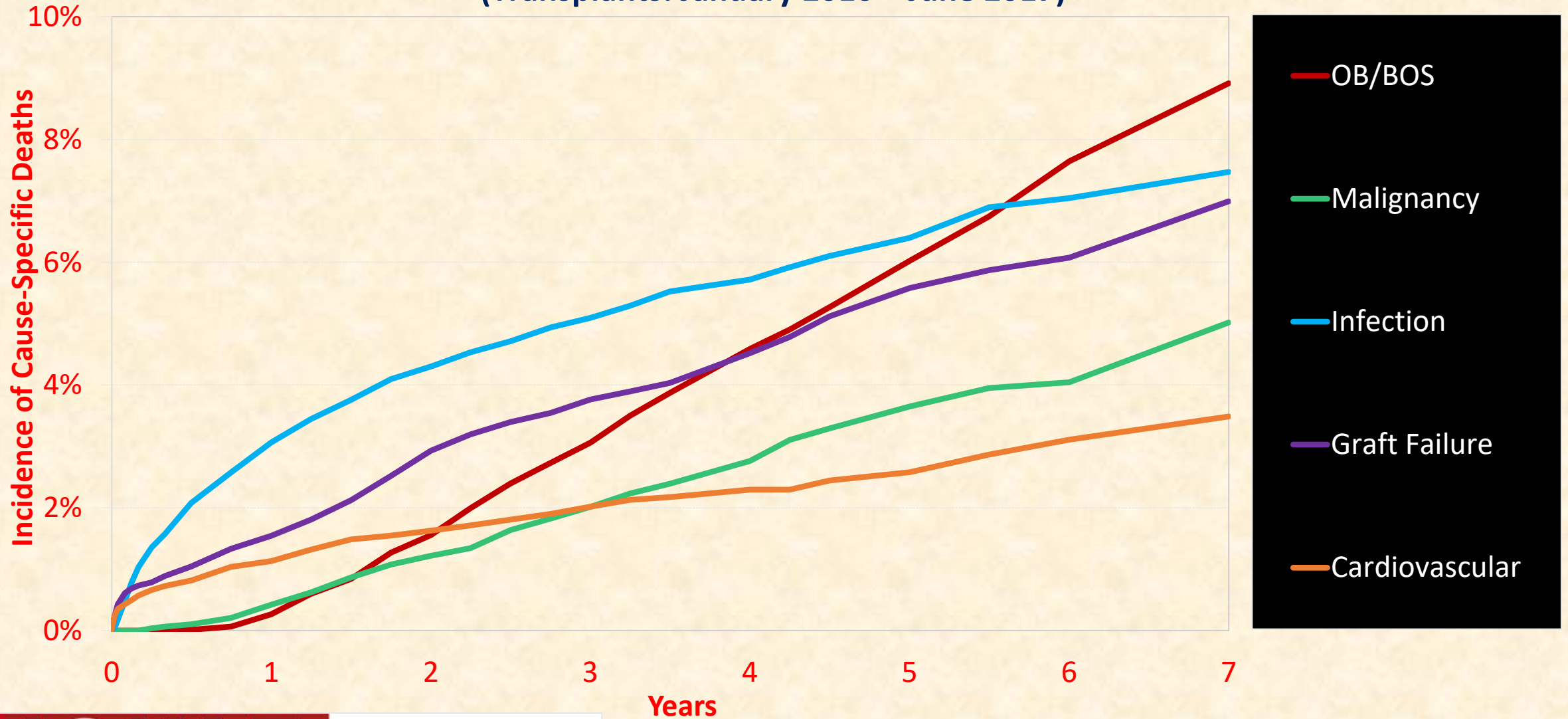
(Transplants: January 1992 – June 2017)



Adult Lung Transplants with COPD

Cumulative Incidence of Leading Causes of Death

(Transplants: January 2010 – June 2017)



Chronic lung allograft dysfunction: Definition, diagnostic criteria, and approaches to treatment—A consensus report from the Pulmonary Council of the ISHLT

Chronic lung allograft dysfunction (CLAD): Clinical manifestations of a range of pathological processes in the airways or parenchyma of lung allograft that lead to significant and persistent deterioration in lung function, and occur > 3 mo after LuTx

Substantial and persistent decline of FEV₁ (>20%) from baseline

- Obstructive pattern: Bronchiolitis Obliterans Syndrome (BOS)
- Restrictive pattern: Restrictive Allograft Syndrome (RAS)

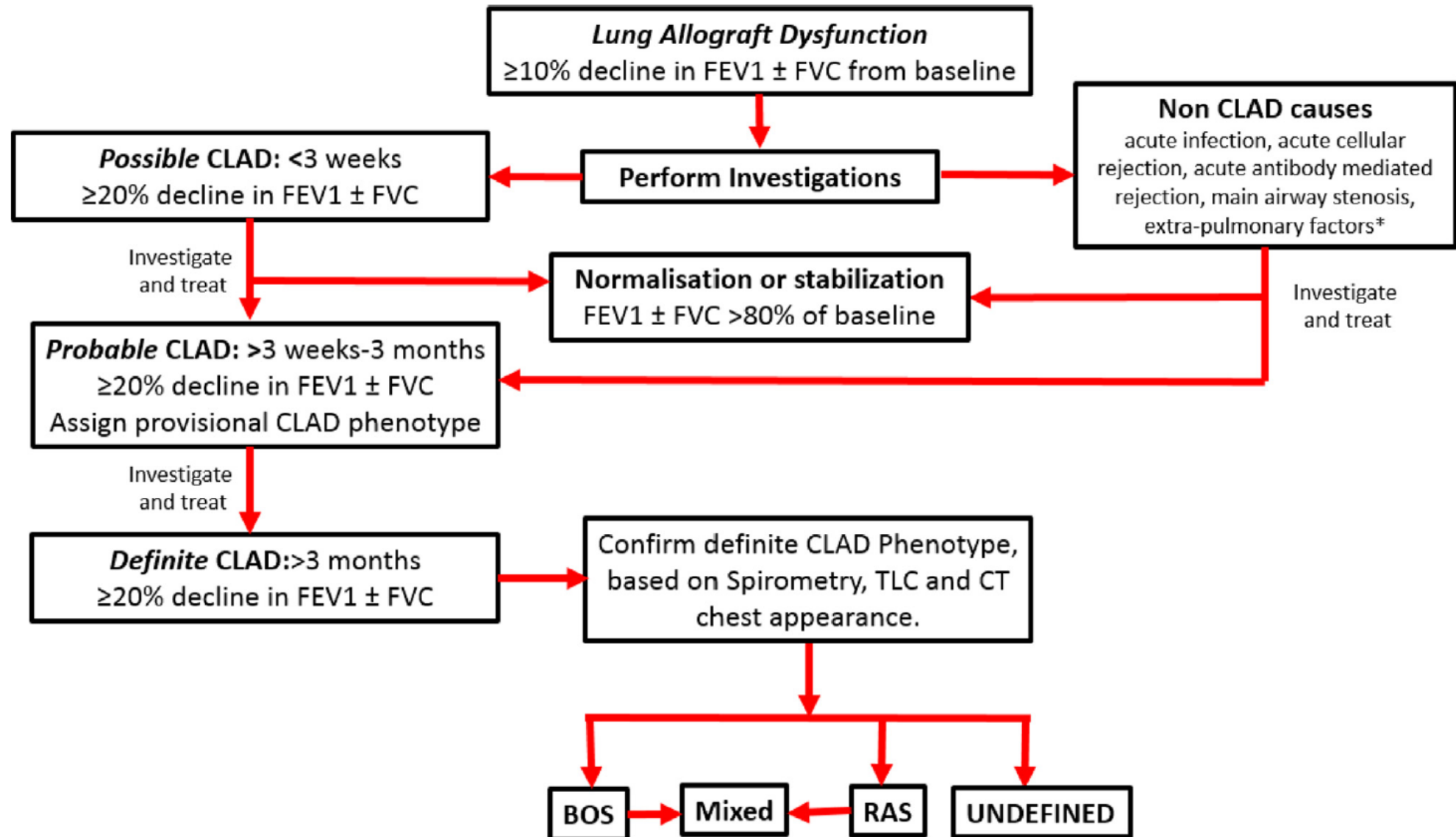


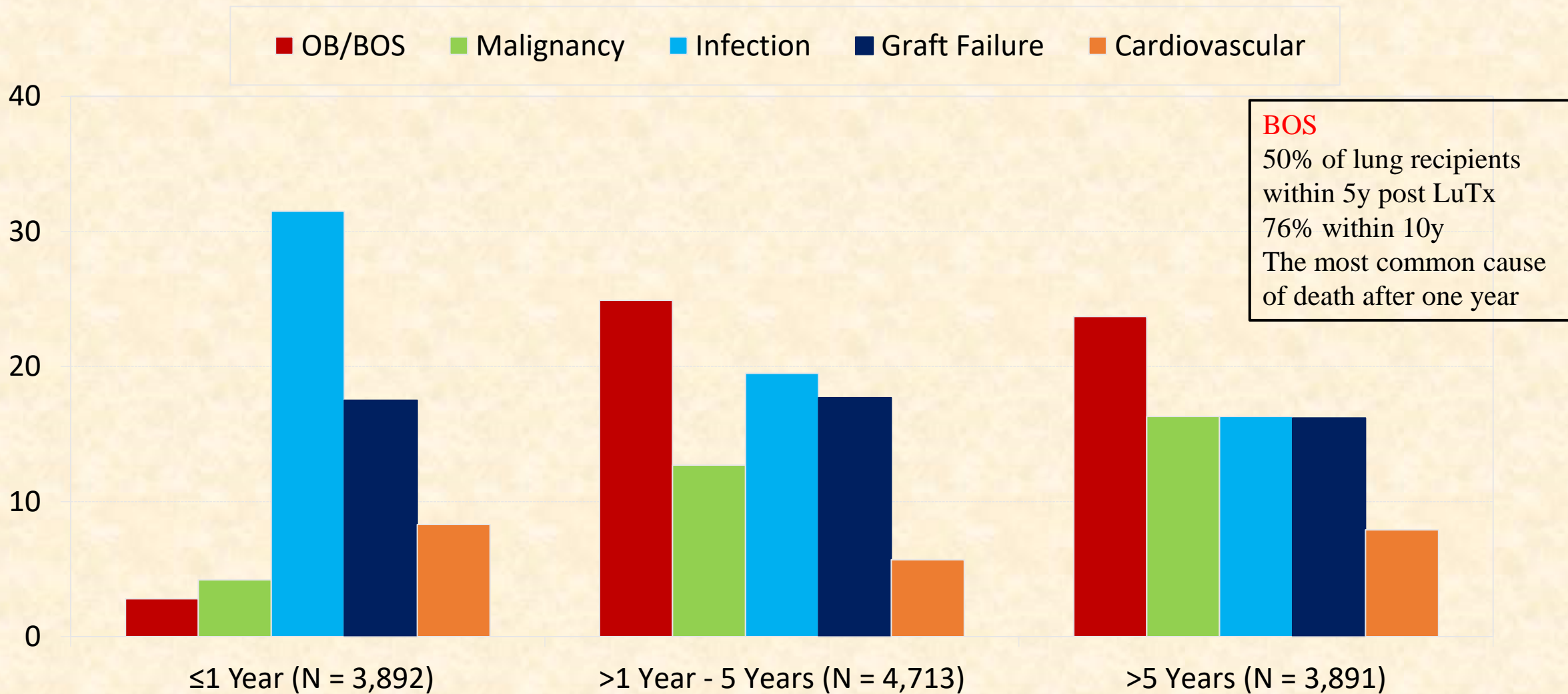
Table 2 CLAD Staging

Stage	Spirometry
CLAD 0	Current FEV ₁ >80% FEV ₁ baseline
CLAD 1	Current FEV ₁ >65–80% FEV ₁ baseline
CLAD 2	Current FEV ₁ >50–65% FEV ₁ baseline
CLAD 3	Current FEV ₁ >35–50% FEV ₁ baseline
CLAD 4	Current FEV ₁ ≤35% FEV ₁ baseline

Adult Lung Transplants with COPD

Relative Incidence of Leading Causes of Death

(Deaths: January 2010 – June 2018)



Adult Lung Transplants (1996-6/2013)

Statistically Significant Risk Factors for BOS within 5 Years Conditional on Survival to Discharge

Continuous Factors

Recipient age (years)

Donor age (years)

Recipient BMI (kg/m²)

Ischemic time (hours)

PA mean (mm/Hg)

Center volume in previous 3 yrs

Recipient bilirubin (mg/dl)

Table 1 Treatment options for chronic rejection after lung transplantation

Treatment	Quality of evidence	Efficacy	Side effects/toxicity
Azithromycin	1 RCT, several case series and observational studies	Improvement in FEV ₁ in 18–60% of those treated (29% in RCT)	Nausea, vomiting, diarrhea
Conversion of cyclosporine to tacrolimus	Case series	Decreased rate of FEV ₁ decline	Increased creatinine, hyperglycemia
Gastric fundoplication	Case series and observational studies	Improvement in FEV ₁ after fundoplication	Perioperative complications, postoperative dysphagia
Montelukast	Case series, observational studies, 1 small RCT	Attenuation of FEV ₁ decline	Well tolerated
Extracorporeal photopheresis	Observational Studies	Improvement in FEV ₁ in 12–30%, attenuation of FEV ₁ decline, possible mortality benefit	Generally well tolerated, citrate reactions
Aerosolized cyclosporine	1 small RCT and case series	Lower rate of CLAD progression, possible mortality benefit	Cough, pharyngeal soreness, acute breathlessness
Cytolytic anti-lymphocyte therapies	Case series and observational studies	Improvement in FEV ₁ in 40%, attenuation of FEV ₁ decline	Serum sickness, cytokine release syndrome, infection
Total lymphoid irradiation	Case series and observational studies	Attenuation of FEV ₁ decline	Leukopenia, infection

Extracorporeal Photapheresis

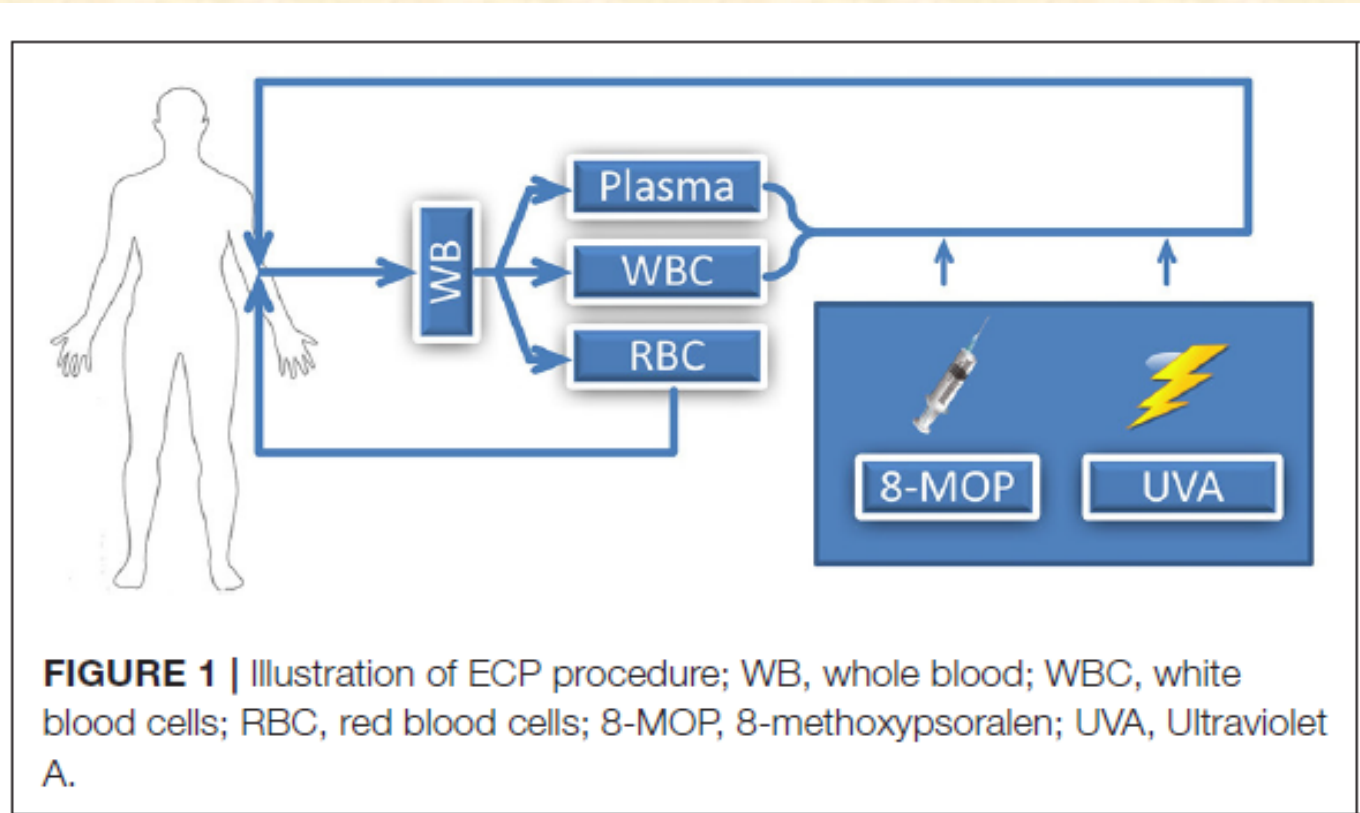
- Cell based immunomodulatory treatment
- Leukapheresis and photodynamic therapy
- FDA approved on 1988: Cutaneous T-cell lymphoma

Blood separation with centrifugation

WBC (buffy coat) treated ex vivo with a photoactive psoralen component

Irradiation with ultraviolet A light

Photoactive WBC return to the patient



- Closed system (FDA approved)
- Open system (different separation instruments)

	Closed system	Open System
Manufacturer	Therakos - UVAR XTS Therakos - CELLEX Fresenius Kabi - AMICUS ECP System	Fresenius Kabi - AMICUS Fresenius Kabi - COM.TEC Terumo BCT - Cobe Spectra Terumo BCT - Spectra Optia
Duration of Treatment (h)	1.5-2	3-4
Venous access	Single or Double	Double
Anticoagulant	Heparin or Citrate	Citrate
Drug Photoactivation System	-	PUVA light system (Macropharma) MACOGENIC (Macropharma) MACOGENICG2 (Macropharma) XUV bag (Macropharma) UVA PIT System (Med Tech Solutions)
FDA approval	Yes, CTCL only	No

GUIDELINES

European dermatology forum: Updated guidelines on the use of extracorporeal photopheresis 2020 – Part 2

R. Knobler,^{1,*}  P. Arenberger,² A. Arun,³ C. Assaf,⁴ M. Bagot,⁵ G. Berlin,⁶ A. Bohbot,⁷ P. Calzavara-Pinton,⁸ F. Child,⁹ A. Cho,¹ L.E. French,¹⁰ A.R. Genney,¹¹ R. Gniadecki,¹² H.P.M. Gollnick,¹³  E. Guenova,¹⁴ P. Jaksch,¹⁵ C. Jantschitsch,¹ C. Klemke,¹⁶ J. Ludvigsson,¹⁷ E. Papadavid,¹⁸ J. Scarisbrick,¹⁹ T. Schwarz,²⁰ R. Stadler,²¹ P. Wolf,²² J. Zic,²³ C. Zouboulis,²⁴ A. Zuckermann,²⁵ H. Greinix²⁶

Indications of ECP

Cutaneous T cell lymphoma (first line treatment)

Graft vs Host disease (second line treatment)

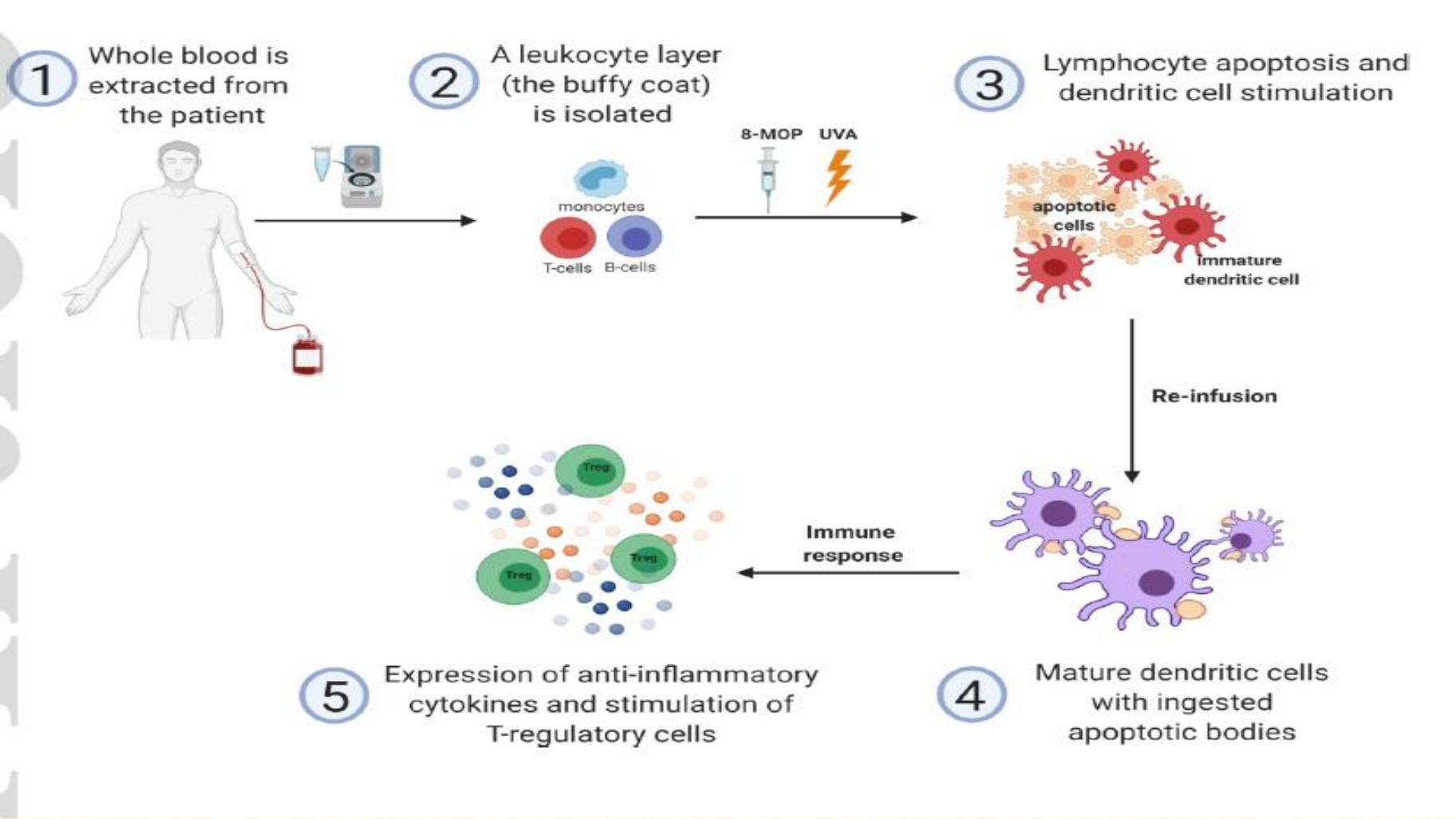
Systemic Sclerosis (Grade of Evidence 2b, Strength of recommendation B)

Solid Organ transplantation (lung, heart, kidney, liver)

Immunomodulatory effects of ECP

- Apoptotic cellular cascade by DNA cross linking (T-lymphocytes)
- After reinfusion: apoptotic leukocytes phagocytosed by immature dendritic cells \longrightarrow antigen-presenting cells
- Increase in anti-inflammatory cytokines
- Decrease in pro-inflammatory cytokines
- Decrease in the cytotoxic activity of NK cells
- Increase in regulatory T-cells
- Differentiation of monocytes to dendritic cells \longrightarrow Interleukin-10

ECP: Mechanism of action



ECP in solid organ transplant recipients

- Increase or stabilization of T_{reg} cells \longrightarrow increased immune tolerance of transplanted tissues
- 5% of WBC are treated but ECP affects the whole immune cells population by its immunomodulatory potencies- transimmunization

Chronic heart or lung rejection

BOS

- Decrease expression of pro-inflammatory cytokines
- Increase level of anti-inflammatory cytokines (T-helper cell type 2)
- Reduction of levels of circulating donor specific HLA antibodies and non HLA antibodies
- Reduction of the rate of decline of FEV₁

TABLE 1.**Summary of clinical evidence of ECP-mediated immunomodulatory effects**

	Immunomodulatory action	Clinical results
T _{reg} cells	<ul style="list-style-type: none"> • Increased T_{reg} cells in 4 patients with chronic heart and lung transplant rejection treated with ECP²² • Increased Foxp3⁺ T_{reg} cells in 2 renal transplant patients after ECP²³ • Slight increase or stabilization in CD4⁺, CD25⁺ T_{reg} cells in 3 of 5 lung transplant recipients treated with ECP²⁴ • Significant increase in T_{reg} cells after ECP treatment in kidney transplant patients (N = 10; P = 0.025)²⁵ • Increased T_{reg} cells in heart transplant patients treated with ECP²⁶ • Clinical response to ECP therapy was paralleled by an increase in T_{reg} cells and a decrease of natural killer cells in a patient with progressive BOS after double-lung transplantation²⁷ 	<ul style="list-style-type: none"> • NR • NR • Clinical stabilization in 3 of 5 patients with BOS²⁴ • Positive trend for increase in GFR in ECP-treated group²⁵ • ~80% of patients responded to ECP therapy with an increase in T_{reg}²⁶ • Clinical response to ECP therapy was paralleled by an increase in T_{reg} cells and a decrease of natural killer cells in a patient with progressive BOS after double-lung transplantation²⁷
Shift in cytokine secretion	<ul style="list-style-type: none"> • Reduced expression of proinflammatory cytokine TNFα in 2 renal transplant patients after ECP²³ • Shift toward anti-inflammatory Th2 cytokine profile in heart transplant patients treated with prophylactic ECP²⁶ • ECP associated with a decline in donor-specific antibody levels, antibodies to lung-associated self-antigens, and circulating levels of proinflammatory cytokines, and increased levels of anti-inflammatory cytokines²⁸ 	<ul style="list-style-type: none"> • NR • 44% of patients responded to ECP therapy with an increase in Th2 cells²⁶ • Immunologic changes associated with a 63% reduction in the rate of decline in FEV₁ over 1 y²⁸

TABLE 2.**Summary Of recent case studies and clinical studies evaluating ECP treatment in BOS**

Study (type)	Patients, n	BOS status	Efficacy/safety
Villanueva et al, 2000 ³⁹ (retrospective case studies)	14	BOS diagnosed by clinical staging (n = 3) and biopsy (n = 11)	<ul style="list-style-type: none"> Stabilized lung function of patients with BOS 0b or BOS 1, but not BOS 2 or BOS 3
Benden et al, 2008 ⁴⁰ (retrospective)	12	Not reported	<ul style="list-style-type: none"> No adverse reactions to ECP Rate of FEV₁ decline was significantly reduced after ECP ($P = 0.011$). Median survival of study cohort: 7.0 y; 4.9 y post-ECP
Morrell et al, 2010 ⁴¹ (retrospective)	60	BOS diagnosed per ISHLT 2002 criteria ⁴⁴	<ul style="list-style-type: none"> Significant difference in FEV₁ rate of decline before and after ECP treatment: 87.1 mL/mo ($P < 0.0001$) Improved lung absolute FEV₁ in 25% patients
Jaksch et al, 2012 ⁴² (prospective)	51	BOS staging per ISHLT classification ⁴⁶	<ul style="list-style-type: none"> Median survival: 7.5 y after transplant, 4.7 y after BOS, 2.6 y after ECP 61% of patients responded ($\pm 5\%$ change FEV₁ from baseline) to ECP. Responders had significantly longer survival compared to nonresponders ($P = 0.001$). ECP responders had significantly longer survival than patients with no ECP treatment ($P = 0.05$).
Greer et al, 2013 ⁴³ (retrospective)	65	RAS, neutrophilic CLAD, and rapid decliners (64 patients deteriorated on azithromycin; 1 had azithromycin contraindications)	<ul style="list-style-type: none"> 54% of patients progressing on azithromycin responded to ECP.
Del Fante et al, 2015 ⁴⁷ (retrospective)	48	BOS diagnosed per ISHLT 2002 criteria ^{4,44}	<ul style="list-style-type: none"> ECP treatment responders ($\pm 10\%$ change FEV₁ from baseline) had longer PFS compared with nonresponders (401 vs 133 days). Among ECP patients, the FEV₁ slope flattened out after initial decline ($P = 0.001$).
Pecoraro et al, 2017 ⁴⁸ (retrospective)	54	BOS diagnosed per ISHLT 2002 criteria ⁴⁴	<ul style="list-style-type: none"> No ECP side effects or complications Stabilization of lung function in 80% of ECP patients.
Moniodis et al, 2017 ⁴⁹ (retrospective)	17	CLAD diagnosed as per published criteria ³ and by analysis of lung biopsies	<ul style="list-style-type: none"> No increase in adverse events or incidence of infections. Significant change of FEV₁ rate of decline by 3 and 6 mo ($P = 0.0005$).
Robinson et al, 2017 ⁵⁰ (retrospective)	15	BOS diagnosed per ISHLT criteria ¹⁵	<ul style="list-style-type: none"> No significant difference between ECP and alemtuzumab for FVC rate, infection and survival Significant decline in lung function after ECP was stopped ($P = 0.003$). 58% of patients died within 12 mo after ECP was stopped.

A prospective interventional study on the use of extracorporeal photopheresis in patients with bronchiolitis obliterans syndrome after lung transplantation

Peter Jaksch, MD,^a Axel Scheed, MD,^a Maya Keplinger, MD,^a Mai-Britt Ernst, MD,^a Theresa Dani, MD,^b Ulrike Just, MD,^b Hesam Nahavandi, MD,^b Walter Klepetko, MD,^a and Robert Knobler, MD^b

From the ^aDepartment of Thoracic Surgery, and the ^bDepartment of Dermatology, University Hospital Vienna, Vienna, Austria.

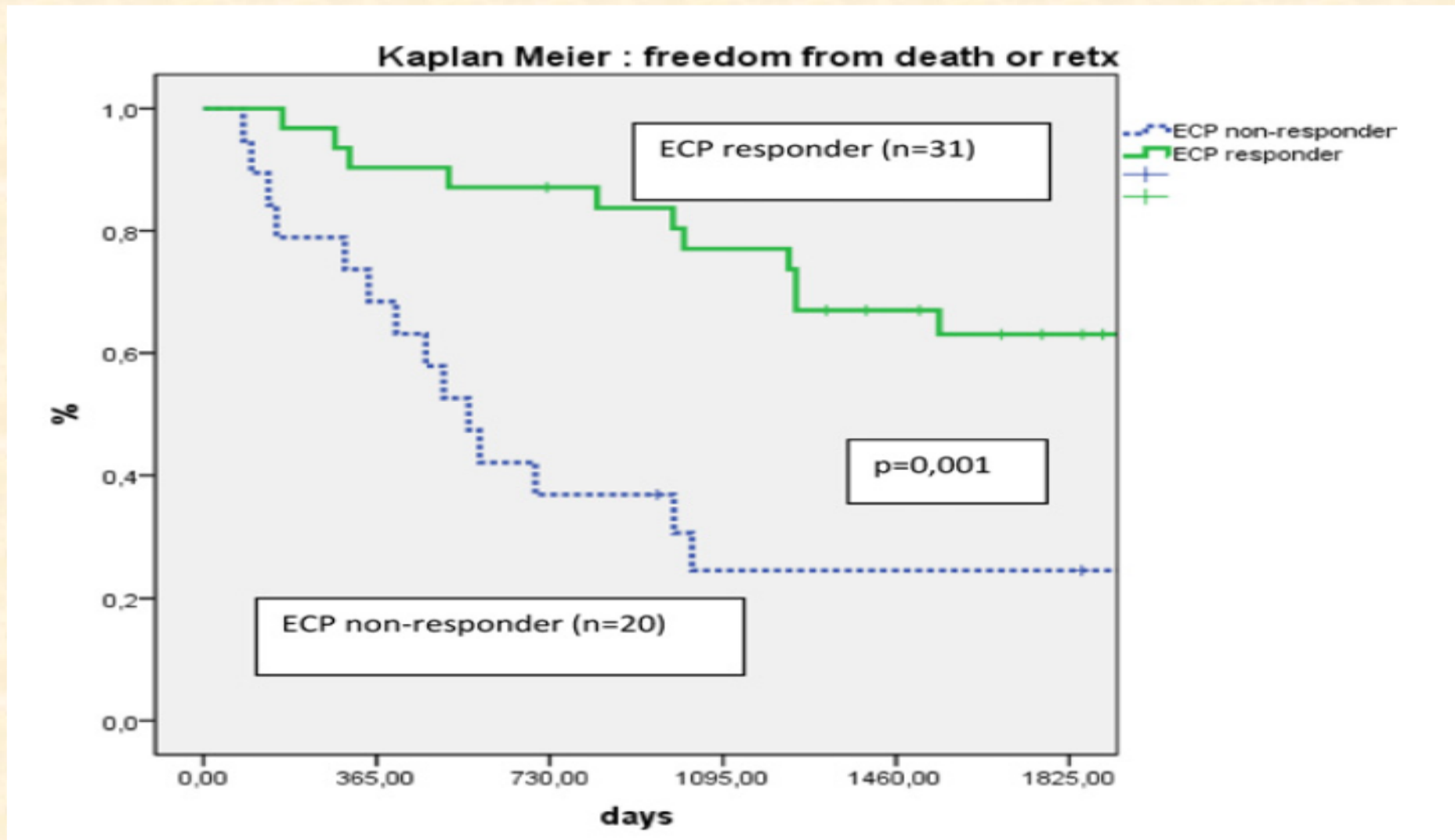
BACKGROUND: The aim of this prospective study was to evaluate the efficacy and safety of extracorporeal photopheresis (ECP) in patients with bronchiolitis obliterans syndrome (BOS) after lung transplantation and to identify factors predicting treatment response.

METHODS: The study was performed at a single center and consisted of a cohort of 1,012 lung transplant recipients (November 1989–June 2010). A total of 194 patients developed BOS after a mean of $1,293 \pm 1,008$ days (range, 99–4,949 days) and received established treatment, and 51 patients received additional ECP.

RESULTS: Thirty-one (61%) of the ECP-treated patients responded to the therapy and showed sustained stabilization (forced expiratory volume in 1 second range, -5% to 5% vs baseline at start of ECP) of lung function over 6 months. Responders to ECP showed significantly greater survival and less need for retransplantation ($p = 0.001$) than non-responders. Factors associated with an inferior treatment response were cystic fibrosis as underlying lung disease and a longer time between transplantation and development of BOS. No side effects were observed after ECP. Compared with BOS patients not treated with ECP, the ECP responders showed an improved graft survival ($p = 0.05$).

CONCLUSIONS: These results confirm and suggest that early use of ECP could be an effective adjunct treatment for patients who develop BOS after lung transplantation.

J Heart Lung Transplant 2012;31:950–7



Large retrospective analysis of CLAD treatment : Vienna, Hannover , Pavia

- Presented at ISHLT 2023 Denver
- Under review

ISHLT 2023

43rd ANNUAL MEETING
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Wednesday, 19 April - Saturday, 22 April
Colorado Convention Center | Denver, CO USA

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Session MINI ORAL 06 - THE EMPIRE STRIKES BACK: Progress in Chronic Lung Allograft Dysfunction (CLAD)

299. A Multicenter Experience with Extracorporeal Photopheresis as Treatment of Clad

April 19, 2023, 6:18 PM - 6:22 PM

Rooms 201-203

Topic:

LUNG-Chronic Lung Allograft Dysfunction (CLAD)

Presenter

A. Benazzo¹, S. Auner², P. Boehm³, S. Schwarz⁴, C. Bagnera⁵, F. Ius⁶, K. Hoetzenecker⁷, F. Meloni⁸, P. Jaksch⁹, M. Greer⁶. ¹Medical University of Vienna, Wien, Austria, ²Medical University of Vienna, Wien, Austria, ³IRCCS Policlinico San Matteo, Pavia, Italy, ⁴Hannover Medical School, Hannover, Germany, ⁵Medical University of Vienna, Wien, Austria, ⁶Policlinico San Matteo di Pavia, Pavia, PV, Italy, ⁷Medical University Vienna, Austria, Wien, Austria.

Disclosures

A. Benazzo: None. M. Greer: Speakers Bureau Fee; Therakos. S. Auner: n/a. P. Boehm: None. S. Schwarz: n/a. C. Bagnera: n/a. F. Ius: Consulting/Advisory Fee; Biotest AG, Research Grant Funds; Biotest AG. K. Hoetzenecker: Consulting/Advisory Fee; Medtronic. F. Meloni: None. P. Jaksch: None.

Methods

- Multicenter retrospective analysis (Vienna, Hannover, Pavia)
- Study period: 1989-2021
- Inclusion criteria:
 - Adult recipients
 - ECP for CLAD
- Primary endpoint: patient survival after ECP initiation
- Definition of response based on FEV1 at initiation of ECP
 - Responders: >10% increase
 - Stable: <10% improvement or <10% worsening
 - Non-responders: decline of >10%

Conclusions

- This analysis includes the **largest CLAD** cohort treated with ECP
- Extracorporeal photopheresis shows **good long-term results** as treatment of CLAD
- Lung **function reserve** at the initiation of ECP and **BOS phenotype** were the two most important predictors of favorable outcome in our cohort
- The presented findings suggest that **early initiation** of ECP may be beneficial in terms of both response and survival.

Safety and tolerability of ECP

- Safe and well tolerated
- Blood loss from extracorporeal circuit
- Hypocalcemia due to anticoagulant
- Mild cytopenia
- Catheter related bacteremia
- Not increased risk of infections
- Not associated with increased mutagenic risk

European dermatology forum: Updated guidelines on the use of extracorporeal photopheresis 2020 – Part 2

- Main indication of ECP after LuTx is CLAD
- Pts with obstructive CLAD seem to respond better
- Pts with earlier onset of CLAD seem to respond better

Treatment schedule

- 2 consecutive days every 2 weeks for 3 months
- If FEV₁ stabilises or improves: every 1 month for 6-12 mo

Response assessment

- Improvement or stabilization of lung function, reduction of the rate of decline



Chronic lung allograft dysfunction: Definition, diagnostic criteria, and approaches to treatment—A consensus report from the Pulmonary Council of the ISHLT

- ECP: A therapeutic option for CLAD (BOS)
- Reduces the rate of decline of lung function
- BOS pts: Slowly progressive FEV₁ decline, increased BAL neutrophilia
- Less successful in rapidly declining BOS pts without BAL neutrophilia and in pts with RAS



Review

Extracorporeal photopheresis for bronchiolitis obliterans syndrome after allogeneic stem cell transplant: An emerging therapeutic approach?

Claudia Del Fante*, Cesare Perotti

Immunohaematology and Transfusion Service, Fondazione IRCCS Policlinico San Matteo, Viale Golgi 19, 27100, Italy

- BOS after HSCT is a manifestation of GVHD in lung
- ECP: few published data in small cohorts of patients
- Considering the dramatic evolution of those pts, stabilization or slowing of lung function decline is response to ECP

Other possible indications of ECP in LTx



Outcome of Extracorporeal Photopheresis as an Add-On Therapy for Antibody-Mediated Rejection in Lung Transplant Recipients

Alberto Benazzo^a Nina Worel^b Stefan Schwarz^a Ulrike Just^c
Anna Nechay^a Christoph Lambers^a Georg Böhmig^d Gottfried Fischer^b
Daniela Koren^b Gabriela Muraközy^a Robert Knobler^c Walter Klepetko^a
Konrad Hoetzenecker^a Peter Jaksch^a

Allograft
dysfunction
DSA
Positive C4d
Positive histology
Mortality: 50-70%

Single centre retrospective analysis (2009-2019)

41 pts with clinical AMP rejection

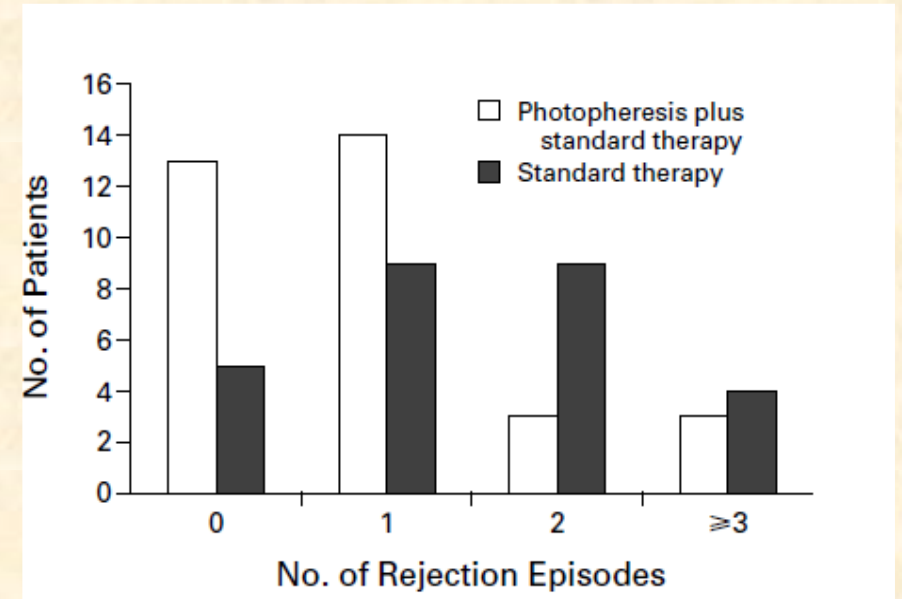
16 received ECP

ECP associated with reduction of dnDSA

Prophylactic use of ECP ???

Heart (1998)

- Addition of ECP to standard triple IS
- Reduced risk of acute rejections
- Not increase of infections
- CMV DNA was detected less frequently in ECP group



The New England Journal of Medicine

PHOTOPHERESIS FOR THE PREVENTION OF REJECTION IN CARDIAC TRANSPLANTATION

MARK L. BARR, M.D., BRUNO M. MEISER, M.D., HOWARD J. EISEN, M.D., RANDALL F. ROBERTS, M.D., UGOLINO LIVI, M.D., ROBERTO DALL'AMICO, M.D., PH.D., RICHARD DORENT, M.D., JOSEPH G. ROGERS, M.D., BRANISLAV RADOVANČEVIĆ, M.D., DAVID O. TAYLOR, M.D., VALLUVAN JEEVANANDAM, M.D., AND CHARLES C. MARBOE, M.D.,
FOR THE PHOTOPHERESIS TRANSPLANTATION STUDY GROUP

Prophylactic Use of Extracorporeal Photopheresis (ECP) – a prospective randomized single center trial (Vienna)

Inclusion time 12/17- 3/21 – minimum 2 year FU

Jaksch P^{1.}, Cho A.^{2.}, Just U^{2.}, Hötzenecker K.^{1.}, Muraközy G.^{1.}, Hielle-Wittmann E.^{1.},
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Wekerle T.^{4.}, Worel N.^{3.}, Benazzo A.^{1.}, Knobler R^{2.}

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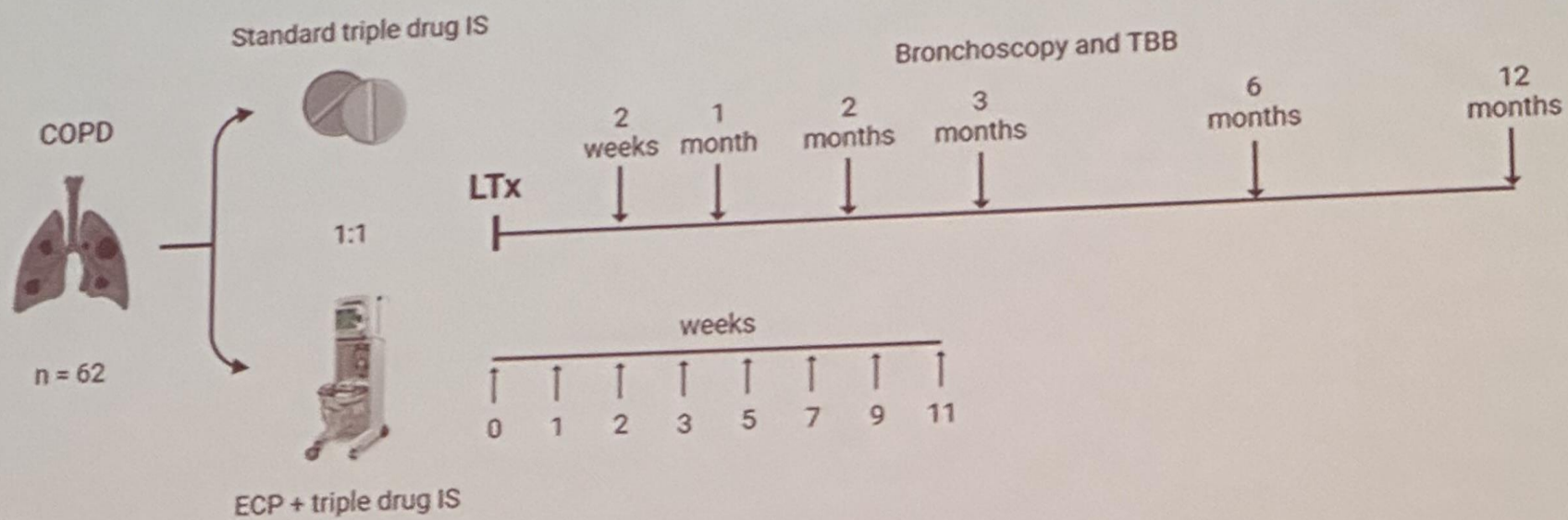
Design and methods

62 COPD recipients (homogenous patient group)

➤ Randomized 1:1 in 2 groups:

1. standard triple-drug IS (tacrolimus, MMF, and prednisone)
2. ECP + standard triple-drug IS

➤ Primary endpoint: incidence of ACR ≥ 1 + cumulative A score



Conclusions

- Patients in the **ECP group** experienced **less** episodes of **histologically-proven ACR and LB**
- Rate of **infections** appeared to be **lower** in the ECP group
- **Incidence of CLAD** in patient receiving ECP was **significantly lower** than standard triple drug IS

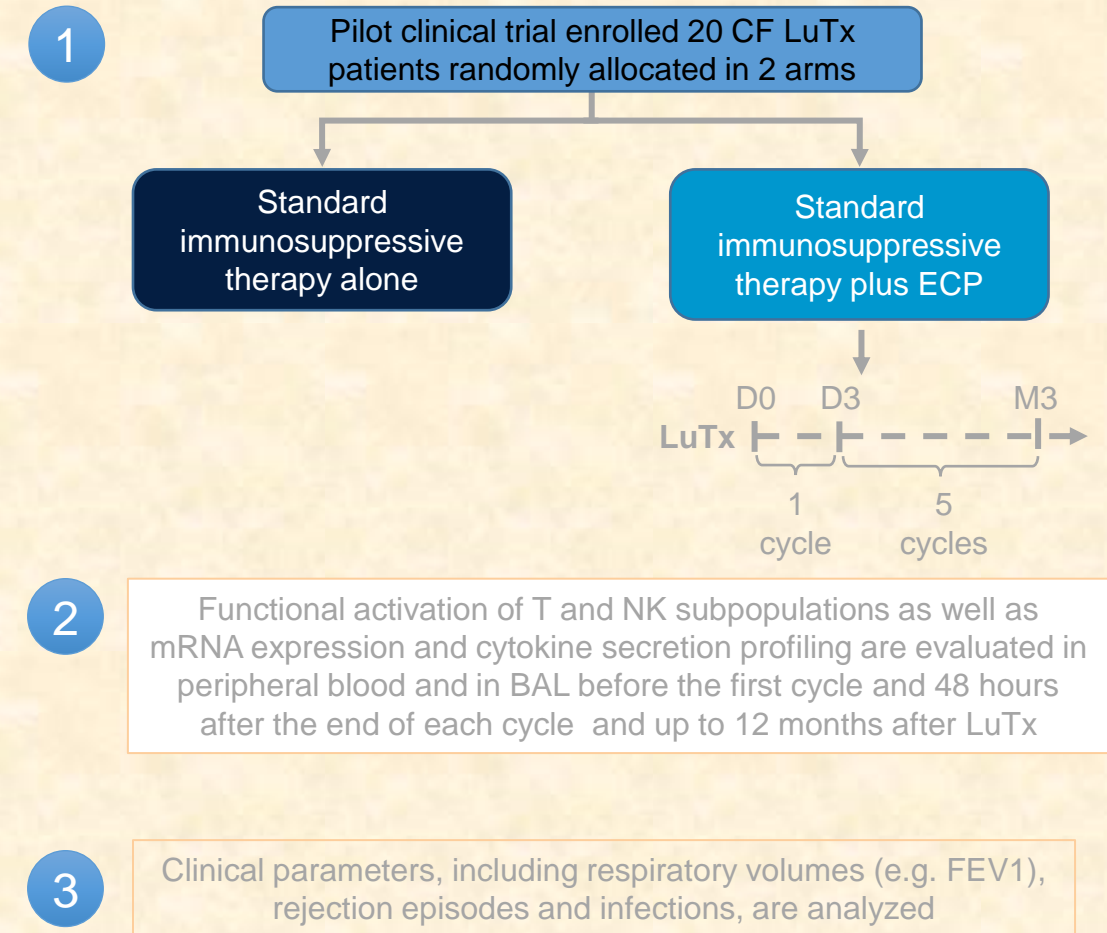
Induction extracorporeal photopheresis stimulates beneficial immune modulation in cystic fibrosis patients undergoing lung transplantation



Background

- CR is the leading cause of late morbidity and mortality upon LuTx
- ECP has emerged as a promising immunomodulatory treatment against rejection
- **Aim:** To perform an in-depth investigation of the immunological effects of induction ECP in LuTx recipients with a diagnosis of CF

Methods



Induction extracorporeal photopheresis stimulates beneficial immune modulation in cystic fibrosis patients undergoing lung transplantation



Results

- ECP was well tolerated with no complications nor opportunistic infections
- Rejection rate was comparable in the two groups
- Notably, a significantly better FEV1 was observed in the ECP group overtime
- Treg lymphocytes and IL10-producing NKs were significantly increased, while Th17 cells were significantly reduced in the ECP group compared to the control
- Cytokine profile showed that ECP reduced pro-inflammatory cytokines (e.g. IL1b, IL6) production, increasing that of anti-inflammatory cytokines (e.g. IL10, IL1RA) both in plasma and BAL

Conclusions

- Induction ECP is associated with immune modulation resulting in improved patients' respiratory performance
- More extensive studies and longer follow-up are needed to verify if ECP-induced immune modulation will have a beneficial effect of organ rejection as well

Our experience

4 pts BOS

- 2 GvHD pts
- 1 pt LuTx – Histiocytosis X
- 1 pt LuTx – Cystic fibrosis

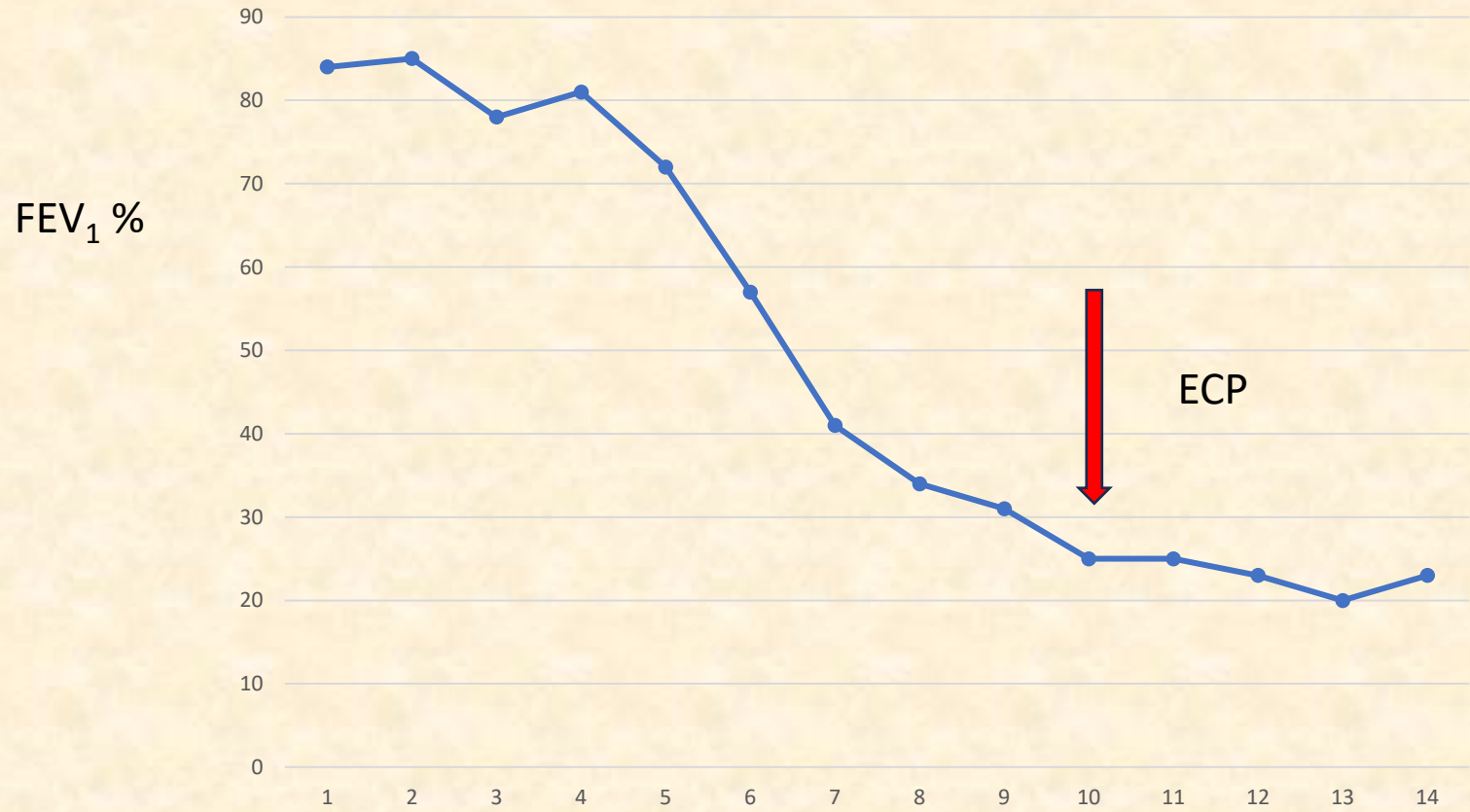
59 yo – LuTx 2008

CLAD (BOS) 2022

Lung function data: FEV1 84% (Feb 2022), 64% (July 2022), 50% (Sept 2022)

ECP: September 2022, twice a month (until March 2023), then once a month, until today (30 ECP, 15 cycles)





Histiocytosis X pt
Lutx Oct 2020
CLAD Sept 2021
ECP Sept 2022





Take home messages

- ECP is a cell – based immunomodulatory treatment combining leukapheresis and photodynamic therapy
- The immunomodulatory mechanisms of ECP are not fully understood but regulatory T cells are key elements
- It is a rational therapeutic approach that may improve the rate of lung function decline and the clinical outcomes in pts with BOS after LTx and GvHD
- Well tolerated therapy with excellent safety profile
- Other possible indications are AMR and prophylactic use early after LTX for an immunosuppressant sparing approach
- Clear need for RCTs



Ευχαριστώ
πολύ